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Leading article

Mycobacteria and Crohn's disease

Recent years have seen a resurgence of interest in the concept of a mycobacterial aetiology for Crohn's disease (CD)[1–5] and the possible use of antituberculous drugs in the condition has been rekindled by scattered case reports.[4,6] Mycobacterial associations with Crohn's disease have long been suspected[7] – the histopathological picture clearly pointing a finger at the genus, but it is only in the last decade that mycobacteria have been isolated from CD tissue.[1,2,8] They have also been isolated from ulcerative colitic and control tissue[3]: this, however, should not come as a surprise. The *Mycobacterium avium-intracellulare* complex (MAIC) is a ubiquitous group of organisms which have recently become notable superinfections in AIDS.[9] This group and some fast growing mycobacteria appear to be saprophytic organisms and can be isolated from healthy individuals[10] and the environment.[11] The isolation of the pathogen *Mycobacterium paratuberculosis* has excited the most interest. This organism is the causative agent of Johne's disease (regional enteritis of ruminants) and to date has been isolated from 7 patients with Crohn's disease in three centres.[2,8,12] The differentiation of this organism from *Mycobacterium avium* has long been a problem, but recently the powerful technique of DNA hybridisation has been used to show that the isolates of *M paratuberculosis* from CD tissues are identical with the pathogenic strains in ruminants, and distinct from MAIC organisms.[13,14] Moreover, this pathogen appears to be highly conserved and its isolation from a disease with a clear animal parallel is intriguing. Johne's disease has been documented in primates[15] and aetiological similarities with CD have been elegantly argued.[16]

The hypothesis therefore is that the clinical picture of CD is a consequence of the host response to infection with *M paratuberculosis*, most likely in the postnatal period,[16] which becomes manifest after a latent period of several years. This would fit with the known familial incidence of CD and with the lack of time and space clustering. The latent period may be comparable with that observed in cows and monkeys, but the course of the disease is not: the animals develop a wasting disease with marked diarrhoea and the organism is recoverable from tissues and faeces. The animal invariably dies.[17] This is in marked contrast to CD, so how might the organism cause the human disease? As with most mycobacteria, it secretes no known specific toxin and the clinical picture must be the result of the immune response to mycobacterial antigens. Whether this response is modulated by mycobacterial products is as yet unclear. The absence of detectable organisms in the tissue may be analogous to the situation in tuberculoid leprosy (with dissemination of *M avium* in the AIDS patient perhaps equating to the lepromatous form), it may be that the organism is simply not present, or that it is present in a variant (L) form. It is notable that the latter is the form in which most of the human isolates are initially

recovered.[18] The serology of mycobacterial infections is a quagmire; however, a study of monkeys infected with *M paratuberculosis*[15] showed that animals without clinical disease had antibodies to the organism, whereas those with disease did not.

Against this background, what is the future for mycobacterial research in CD? First, a rapid culture system must be developed to facilitate the isolation of these organisms and to allow testing of more relevant antimycobacterial drugs. Contemporary antituberculous agents need to be used in multiple combination to be effective against atypical mycobacterial infections: they are woefully inadequate when these confront the AIDS patient. Success with such combinations in CD has been reported,[19] but the evidence of a controlled trial is so far lacking. Second, the organisms must be sought in the tissues by *in situ* hybridisation, or DNA-DNA hybridisation in solution with the signal amplified by polymerase chain reactions. If these avenues are fruitful, intestinal resection for CD may follow the fate of thoracoplasty.

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